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Phenotypic Allele Detail

Your Input

Allele
Symbol: Trp53^{tm1Tyj}
Name: targeted mutation 1, Tyler Jacks
ID: MGI:1857263

Synonyms p53-, p53^{delta}, p53^{null}, Trp53-

Allele details
Allele Type: Targeted (knock-out)
Strain of Origin: 129S2/SvPas
ES Cell Line: D3
ES Cell Line Strain: 129S2/SvPas
Mutation: Disruption caused by insertion of vector
A neomycin cassette replaced 40% of the coding sequences beginr (upstream of the translation start site) and extending into exon 6.
Gene Expression in Trp53^{tm1Tyj} mutants (31 assay results)
International Mouse Strain Resource: (Search for IMSR strains w mutations)
Mouse Models of Human Diseases: (See Below)
References and Additional Notes: (See Below)

Gene information
Symbol: Trp53
Name: transformation related protein 53
Chromosome: 11
Genetic Position: 39.0 cM, cytoband B2-C
Genome Coordinates: 69305640-69317530 bp, + strand (From I of NCBI Build 34)
Human Ortholog: TP53

Phenotypes **Phenotypic details for all genotypes that include at least one Trp!**

Phenotype	Allelic Composition	Genotype Genetic Backgroı
Go To	Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	involves: 129/Sv * C57BL/6
Go To	Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	involves: 129S2/SvPas
Go To	Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	involves: 129S2/SvPas * C57B
Go To	Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	involves: C57BL/6
Go To	Trp53^{tm1Tyj}/Trp53^{+}	involves: 129/Sv * C57BL/6
Go To	Trp53^{tm1Tyj}/Trp53^{+}	involves: 129S2/SvPas
Go To	Trp53^{tm1Tyj}/Trp53^{+}	involves: 129S2/SvPas * C57B
Go To	Trp53^{tm1Tyj}/Trp53^{+}	involves: C57BL/6
Go To	Trp53^{tm1Tyj}/Trp53$^{tm2.1Tyj}$	involves: 129S2/SvPas * 129S
Go To	Trp53^{tm1Tyj}/Trp53$^{tm3.1Tyj}$	involves: 129S2/SvPas * 129S
Go To	Terf1^{tm1Tdl}/Terf1^{tm1Tdl} Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	129/Sv
Go To	Ccne1^{tm1Jro}/? Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	either: (involves: 129S2/SvPas 129S4/SvJaeSor * C57BL/6J) (129S2/SvPas * 129S4/SvJaeS(C57BL/6J)
Go To	Motp1$^{CE/J}$/Motp1$^{CE/J}$ Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	involves: 129-Trp53^{tm1Tyj}/J * (
Go To	Motp1$^{CE/J}$/Motp1$^{CE/J}$ Trp53^{tm1Tyj}/Trp53^{+}	involves: 129-Trp53^{tm1Tyj}/J * (
Go To	Thbs1^{tm1Hyn}/Thbs1^{tm1Hyn} Trp53^{tm1Tyj}/Trp53^{+}	involves: 129/Sv * C57BL/6
Go To	Thbs1^{tm1Hyn}/Thbs1^{tm1Hyn} Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	involves: 129/Sv * C57BL/6

The Jackson Laboratory
last database update
11/15/2005
MGI 3.4

Go To	$Dph1^{tm2Bhr}/Dph1^{tm2Bhr}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129/Sv * C57BL/6
Go To	$Dph1^{tm2Bhr}/Dph1^{+}$ $Trp53^{tm1Tyj}/Trp53^{+}$	involves: 129/Sv * C57BL/6
Go To	$Nf1^{tm1Tyj}/Nf1^{+}$ $Trp53^{tm1Tyj}/Trp53^{+}$	involves: 129/Sv * C57BL/6
Go To	$Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$ $Tsg101^{tm1Mak}/Tsg101^{tm1Mak}$	involves: 129P3/J * C57BL/6 *
Go To	$Brca1^{tm1Arge}/Brca1^{tm1Arge}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S/SvEv * 129S2/ C57BL/6
Go To	$Brca2^{tm1Arge}/Brca2^{tm1Arge}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S/SvEv * 129S2/ C57BL/6
Go To	$Bard1^{tm1Thl}/Bard1^{tm1Thl}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S1/Sv
Go To	$Rad50^{tm2Jpt}/Rad50^{tm2Jpt}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S2/SvPas * 129S 129S7/SvEvBrd * C57BL/6
Go To	$Tfdp1^{tm1Lill}/Tfdp1^{tm1Lill}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S2/SvPas * C57B
Go To	$Tfdp1^{tm1Lill}/Tfdp1^{+}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S2/SvPas * C57B
Go To	$Prdm2^{tm1Shg}/Prdm2^{tm1Shg}$ $Trp53^{tm1Tyj}/Trp53^{+}$	involves: 129S2/SvPas * C57B
Go To	$Rb1^{tm1Tyj}/Rb1^{+}$ $Trp53^{tm1Tyj}/Trp53^{+}$	involves: 129S2/SvPas * C57B
Go To	$Rag2^{tm1Fwa}/Rag2^{tm1Fwa}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S2/SvPas * C57B
Go To	$Rag2^{tm1Fwa}/Rag2^{+}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S2/SvPas * C57B
Go To	$Prkdc^{scid}/Prkdc^{+}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S2/SvPas * C57B
Go To	$Nf1^{tm1Tyj}/?$ $Trp53^{tm1Tyj}/?$ $Mastr^{129S4/SvJae}/?$	involves: 129S4/SvJae * C57B
Go To	$Nf1^{tm1Tyj}/?$ $Trp53^{tm1Tyj}/?$ $Mastr^{C57BL/6J}/?$	involves: 129S4/SvJae * C57B
Go To	$Mdm2^{tm1Glo}/Mdm2^{tm1Glo}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S7/SvEvBrd * C5
Go To	$Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$ $Xrcc1^{tm1Rpe}/Xrcc1^{tm1Rpe}$	involves: 129X1/SvJ
Go To	Tg(Actb-NOTCH1)1Shn/0 Tg(Nes-cre)1Kln/0 $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: C57BL/6J
Go To	Tg(Actb-NOTCH1)1Shn/0 Tg(Nes-cre)1Kln/0 $Trp53^{tm1Tyj}/Trp53^{+}$	involves: C57BL/6J
Go To	$Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$ $Xrcc4^{tm1Fwa}/Xrcc4^{tm1Fwa}$	Not Specified

Allelic Composition	Genetic Background
$Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129/Sv * C57BL/6

life span/aging

premature death (J:87501, J:72391)
- 90% had succumbed to tumors and died by 7 months of a
- average life span 160 days (J:72391)

tumorigenesis
increased tumor incidence (J:72391)
- adenoma (J:72391)
- carcinoma (J:72391)
- lymphoma (J:72391)
  - thymic lymphoma (J:87501)
    - 75% of observed tumors were thymic lym
- sarcoma (J:72391)

cellular
abnormal apoptosis (J:87501)
chromosomal instability (J:87501)
- aneuploidy

Allelic Composition **Genetic Background**

$Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$ involves: 129S2/SvPas

lethality/embryonic-perinatal
embryonic lethality (J:95316)
- a slight decrease is seen in the number of females born

life span/aging
premature death (J:95316)
- mean life span is 4.4 months

tumorigenesis
increased tumor incidence (J:95316)
- 32% have multiple tumors

T cell derived lymphoma (J:95316)
- 66% of homozygotes display hematological malign primarily T cell lymphomas

hemangiosarcoma (J:95316)
- the incidence of hemangiosarcomas is 32% compa $Trp53^{tm1Tyj}$ $Trp53^{tm2.1Tyj}$ transheterozygotes

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Allelic Composition **Genetic Background**

$Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$ involves: 129S2/SvPas * C57BL/6

tumorigenesis
increased tumor incidence (J:17728)
- most mice dead by 6 months
- predominantly lymphomas with sarcomas and teratomas

lymphoma (J:17728)
sarcoma (J:17728)
teratoma (J:17728)

Allelic Composition **Genetic Background**

$Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$ involves: C57BL/6

life span/aging
premature death (J:95318)
- homozygous mutants die between ~50 to 250 days after b

tumorigenesis

lymphoma (*J:95318*)
- 56% of homozygous nulls developed lymphomas

sarcoma (*J:95318*)
- 40% of homozygous nulls developed sarcomas

cellular

decreased sensitivity to gamma-irradiation (*J:95318*)
- irradiated E13.5 heterozygous embryos showed no eviden in the hypothalamus compared to wildtype and heterozygc showed a high number of apoptotic cells

increased cell proliferation (*J:95318*)
- MEFs initially did not show any significant differences in gr by day 4, grew more rapidly than wildtype or heterozygou

Allelic Composition	Genetic Background
Trp53^{tm1Tyj}/Trp53^{+}	involves: 129/Sv * C57BL/6

tumorigenesis

increased tumor incidence (*J:72391*)
- adenoma (*J:72391*)
- carcinoma (*J:72391*)
- lymphoma (*J:72391*)
- sarcoma (*J:72391*)

Allelic Composition	Genetic Background
Trp53^{tm1Tyj}/Trp53^{+}	involves: 129S2/SvPas

life span/aging

premature death (*J:95316*)
- mean life span is 15.4 months

tumorigenesis

increased tumor incidence (*J:95316*)
- 19% have multiple tumors compared to 44% of Trp53$^{tm3.}$ heterozygotes

carcinoma (*J:95316*)
- 4 of 37 develop low grade carcinomas including 1 differentiated lung carcinoma

cellular

increased cell proliferation (*J:95316*)
- a larger fraction of MEFs are in S phase compared to wild t

Allelic Composition	Genetic Background
Trp53^{tm1Tyj}/Trp53^{+}	involves: 129S2/SvPas * C57BL/6

tumorigenesis

increased tumor incidence (*J:17728*)
- age of onset 9 months

lymphoma (*J:17728*)

sarcoma (*J:17728*)

Allelic Composition	Genetic Background
Trp53^{tm1Tyj}/Trp53^{+}	involves: C57BL/6

life span/aging

premature death (*J:95318*)
- heterozygous mutants die between 150 to 750 days after

tumorigenesis
- carcinoma (*J:95318*)
  - 12% of heterozygous mutants developed carcinomas, whi homozygotes
- lymphoma (*J:95318*)
  - 32% of heterozygous mutants developed lymphomas
- sarcoma (*J:95318*)
  - 56% of heterozygous mutants developed sarcomas

Allelic Composition	Genetic Background
$Trp53^{tm1Tyj}/Trp53^{tm2.1Tyj}$	involves: 129S2/SvPas * 129S4/SvJae

lethality/embryonic-perinatal
- embryonic lethality (*J:95316*)
  - a slight decrease is seen in the number of females born

life span/aging
- premature death (*J:95316*)
  - mean life span is 4.5 months

tumorigenesis
- increased tumor incidence (*J:95316*)
  - 57% have multiple tumors, significantly more than in Trp5 homozygotes (32%)
    - carcinoma (*J:95316*)
      - carcinomas are seen in 16% of transheterozygotes carcinomas showing signs of invasion, metastasis, features of advanced human carcinomas
      - most carcinomas are derived from epithelial cells
    - T cell derived lymphoma (*J:95316*)
      - a slight decrease in hematological malignancies (p lymphomas) is seen compared to $Trp53^{tm1Tyj}$ hom compared to 66%)
    - hemangiosarcoma (*J:95316*)
      - the incidence of hemangiosarcomas is increased to compared to 32% in $Trp53^{tm1Tyj}$ homozygotes anc are highly aggressive

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Allelic Composition	Genetic Background
$Trp53^{tm1Tyj}/Trp53^{tm3.1Tyj}$	involves: 129S2/SvPas * 129S4/SvJae

lethality/embryonic-perinatal
- embryonic lethality (*J:95316*)
  - a slight decrease is seen in the number of females born

life span/aging
- premature death (*J:95316*)
  - mean life span is 4.6 months

tumorigenesis
- increased tumor incidence (*J:95316*)
  - 43% have multiple tumors
    - carcinoma (*J:95316*)
      - carcinomas are seen in 18% of transheterozygotes carcinomas showing signs of invasion, metastasis, features of advanced human carcinomas
      - most carcinomas are derived from epithelial cells
    - T cell derived lymphoma (*J:95316*)
      - a slight decrease in hematological malignancies (p lymphomas) is seen compared to $Trp53^{tm1Tyj}$ hom

compared to 66%)

Allelic Composition	Genetic Background
Terf1^{tm1Tdl}/Terf1^{tm1Tdl} Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	129/Sv

lethality/embryonic-perinatal
embryonic lethality before somite formation (*J:85440*)
- no homozygotes were born
- timing of lethality was somewhat attenuated
- undersized surviving embryos found at E7-7.5
- 2 surviving embryos at E8-8.5

embryogenesis
abnormal extraembryonic tissue morphology (*J:85440*)
- extraembryonic structures generally disorganized

Allelic Composition	Genetic Background
Ccne1^{tm1Jro}/? Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	either: (involves: 129S2/SvPas * 129S4/SvJaeS or (involves: 129S2/SvPas * 129S4/SvJaeSor C57BL/6J)

cellular
increased cell proliferation (*J:99695*)
- cell proliferation in double mutant MEFs is increased comp homozygous null for Trp53 alone

tumorigenesis
increased tumor incidence (*J:99695*)
- mean tumor-free survival is reduced to 145 days compare in mice homozygous null for Trp53 alone

Allelic Composition	Genetic Background
Motp1$^{CE/J}$/Motp1$^{CE/J}$ Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	involves: 129-Trp53^{tm1Tyj}/J * CE/J

lethality/embryonic-perinatal
embryonic lethality (*J:97137*)
- increased embryonic lethality
- ratio distortion

Allelic Composition	Genetic Background
Motp1$^{CE/J}$/Motp1$^{CE/J}$ Trp53^{tm1Tyj}/Trp53^{+}	involves: 129-Trp53^{tm1Tyj}/J * CE/J

lethality/embryonic-perinatal
embryonic lethality (*J:97137*)
- increased embryonic lethality
- ratio distortion

Allelic Composition	Genetic Background
Thbs1^{tm1Hyn}/Thbs1^{tm1Hyn} Trp53^{tm1Tyj}/Trp53^{+}	involves: 129/Sv * C57BL/6

life span/aging
premature death (*J:72391*)
- average life span 426 days

tumorigenesis

increased tumor incidence (*J:72391*)
adenoma (*J:72391*)
carcinoma (*J:72391*)
lymphoma (*J:72391*)
sarcoma (*J:72391*)

Allelic Composition	Genetic Background
$Thbs1^{tm1Hyn}/Thbs1^{tm1Hyn}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129/Sv * C57BL/6

life span/aging
premature death (*J:72391*)
- average life span 149 days

tumorigenesis
increased tumor incidence (*J:72391*)
adenoma (*J:72391*)
carcinoma (*J:72391*)
lymphoma (*J:72391*)
sarcoma (*J:72391*)
- increased incidence of sarcomas overall, but decre of osteosarcomas

Allelic Composition	Genetic Background
$Dph1^{tm2Bhr}/Dph1^{tm2Bhr}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129/Sv * C57BL/6

lethality/embryonic-perinatal
embryonic lethality during organogenesis (*J:88090*)
- 30-50% of embryos die between E11.5 and E13.5

neonatal lethality (*J:88090*)
- homozygotes die soon after birth

cellular
cellular phenotype (*J:88090*)
- proliferation defect in cultured MEFs rescued by this genot

Allelic Composition	Genetic Background
$Dph1^{tm2Bhr}/Dph1^{+}$ $Trp53^{tm1Tyj}/Trp53^{+}$	involves: 129/Sv * C57BL/6

tumorigenesis
increased tumor incidence (*J:88090*)
- tumors develop much quicker in this genotype
- latency of 52 weeks as opposed to 70 weeks

Allelic Composition	Genetic Background
$Nf1^{tm1Tyj}/Nf1^{+}$ $Trp53^{tm1Tyj}/Trp53^{+}$	involves: 129/Sv * C57BL/6

life span/aging
premature death (*J:58876*)
- cis-double heterozygotes die by 5 months of age and trans heterozygotes survive to the average age of 10 months

tumorigenesis
increased tumor incidence (*J:58876*)
- cis-double heterozygotes exhibit greater incidence of tumo double heterozygotes

malignant peripheral nerve sheath tumors (J:58
- develop in cis-double heterozygotes, usually correl of one chromosome

sarcoma (J:58876)
- developed in both cis- and trans-double heterozyg
- sarcomas in trans-double heterozygotes were simi found in mice with either single mutation and were correlated with loss of one chromosome

Allelic Composition	Genetic Background
Trp53^{tm1Tyj}/Trp53^{tm1Tyj} Tsg101^{tm1Mak}/Tsg101^{tm1Mak}	involves: 129P3/J * C57BL/6 * CD-1

lethality/embryonic-perinatal
embryonic lethality during organogenesis (J:67553)
- die between E8.5 and E10.5

embryogenesis
reduced embryo size (J:67553)
- larger than Tsg101^{tm1Mak} homozygous mutant mice at E8.

growth/size
reduced embryo size (J:67553)
- larger than Tsg101^{tm1Mak} homozygous mutant mice at E8.

Allelic Composition	Genetic Background
Brca1^{tm1Arge}/Brca1^{tm1Arge} Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	involves: 129S/SvEv * 129S2/SvPas * C57BL/

lethality/embryonic-perinatal
embryonic lethality (J:40594)

embryogenesis
abnormal extraembryonic tissue morphology (J:40594)

growth/size
growth/weight/body size abnormality: embryonic (J:40

nervous system
abnormal neural tube morphology/development (J:405

Allelic Composition	Genetic Background
Brca2^{tm1Arge}/Brca2^{tm1Arge} Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	involves: 129S/SvEv * 129S2/SvPas * C57BL/

lethality/embryonic-perinatal
embryonic lethality (J:40594)

growth/size
growth/weight/body size abnormality: embryonic (J:40

nervous system
abnormal neural tube morphology/development (J:405

Allelic Composition	Genetic Background
Bard1^{tm1Thl}/Bard1^{tm1Thl} Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	involves: 129S1/Sv

lethality/embryonic-perinatal
embryonic lethality (*J:84329*)
- survived through E9.5

tumorigenesis
altered tumor susceptibility/resistance (*J:84329*)

cellular
chromosomal instability (*J:84329*)
- 44% of mitotic spreads showed abnormal chromosome nu reduced

embryogenesis
reduced embryo size (*J:84329*)
- developmentally retarded by E9.5

growth/size
reduced embryo size (*J:84329*)
- developmentally retarded by E9.5

nervous system
open neural tube (*J:84329*)
- seen at E9.5

Allelic Composition	Genetic Background
$Rad50^{tm2Jpt}/Rad50^{tm2Jpt}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S2/SvPas * 129S6/SvEvTac * 12 C57BL/6

life span/aging
premature death (*J:78820*)
- mean age of death is 4.5 months

tumorigenesis
altered tumor susceptibility/resistance (*J:78820*)
- acceleration of tumorigenesis
  thymic lymphoma (*J:78820*)

immune system
immune system phenotype (*J:78820*)
- B cell numbers increased 5-20 fold compared to $Rad50^{tm2}$ mice

reproductive system
abnormal testis morphology (*J:78820*)
- suppression of testicular apoptosis
- normal meiotic progression

endocrine/exocrine glands
abnormal testis morphology (*J:78820*)
- suppression of testicular apoptosis
- normal meiotic progression

Allelic Composition	Genetic Background
$Tfdp1^{tm1Lll}/Tfdp1^{tm1Lll}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S2/SvPas * C57BL/6

lethality/embryonic-perinatal
embryonic lethality (*J:81580*)

Allelic Composition	Genetic Background
$\frac{Tfdp1^{tm1Lll}}{Trp53^{tm1Tyj}}/\frac{Tfdp1^{+}}{Trp53^{tm1Tyj}}$	involves: 129S2/SvPas * C57BL/6

lethality/embryonic-perinatal

embryonic lethality (*J:81580*)

- incomplete penetrance, ~50% survive to adulthood

nervous system

exencephaly (*J:81580*)

- observed at E13.5, and incompletely penetrant

Allelic Composition	Genetic Background
$\frac{Prdm2^{tm1Shq}}{Trp53^{tm1Tyj}}/\frac{Prdm2^{tm1Shq}}{Trp53^{+}}$	involves: 129S2/SvPas * C57BL/6

life span/aging

premature death (*J:71406*)

- mean age of survival was 415 days vs. mice heterozygous or homozygous Prdm2 alone, which survived to ~550 days

tumorigenesis

increased tumor incidence (*J:71406*)

- of types similar to those found in mice homozygous for Prc

Allelic Composition	Genetic Background
$\frac{Rb1^{tm1Tyj}}{Trp53^{tm1Tyj}}/\frac{Rb1^{+}}{Trp53^{+}}$	involves: 129S2/SvPas * C57BL/6

life span/aging

premature death (*J:19542*)

- the mean age of survival of double heterozygotes is slightl relative to mice heterozygous for $Rb1^{tm1Tyj}$ alone (9 mont months)

tumorigenesis

increased tumor incidence (*J:19542*)

- 8% of a total of 12 individual double heterozygotes analyz bronchial hyperplasia; neither lymphomas nor retinal dysp observed
- each of 67 double heterozygotes analyzed developed pituit the intermediate lobe; ~75% of these mice also developec thyroid tumors
- in nearly all double heterozygotes with pituitary and thyroi wild-type allele of Rb1 is lost whereas the wild-type allele retained
- one of 7 individual double heterozygotes analyzed displaye pinealoblastoma (not detected in single heterozygotes); th alleles of both Rb1 and Trp53 were lost in this piineal tumc

carcinoma (*J:19542*)

- 14% of a total of 14 individual double heterozygot displayed islet cell carcinomas (not detected in sin heterozygotes)
- notably, the wild-type alleles of both Rb1 and Trp5 tumors of the islet cells of the pancreas

sarcoma (*J:19542*)

- 6% of a total of 67 individual double heterozygote displayed anaplastic sarcomas
- such tumors were shown to be more aggressive ar earlier age than those occurring in single $Trp53^{tm1}$ heterozygotes

- notably, the wild-type alleles of both Rb1 and Trp5 these anaplastic sarcomas

leiomyosarcoma (*J:19542*)

- one of 7 individual double heterozygotes a displayed a leiomyosarcoma

Allelic Composition	Genetic Background
$Rag2^{tm1Fwa}/Rag2^{tm1Fwa}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S2/SvPas * C57BL/6 * MF1

life span/aging

premature death (*J:47667*)

- death occurs between 7-9 months of age

tumorigenesis

thymic lymphoma (*J:47667*)

- thymoma (67% incidence)

Allelic Composition	Genetic Background
$Rag2^{tm1Fwa}/Rag2^{+}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S2/SvPas * C57BL/6 * MF1

life span/aging

premature death (*J:47667*)

- death occurs between 7-9 months of age

tumorigenesis

thymic lymphoma (*J:47667*)

- thymoma (55% incidence)

Allelic Composition	Genetic Background
$Prkdc^{scid}/Prkdc^{+}$ $Trp53^{tm1Tyj}/Trp53^{tm1Tyj}$	involves: 129S2/SvPas * C57BL/6J

life span/aging

premature death (*J:47667*)

- animals became ill and died around 7 months

tumorigenesis

thymic lymphoma (*J:47667*)

- 60% incidence of thymoma

Allelic Composition	Genetic Background
$Nf1^{tm1Tyj}/?$ $Trp53^{tm1Tyj}/?$ $Mastr^{129S4/SvJae}/?$	involves: 129S4/SvJae * C57BL/6J

tumorigenesis

resistance to tumor development (*J:92444*)

- astrocytoma resistance

Allelic Composition	Genetic Background
$Nf1^{tm1Tyj}/?$ $Trp53^{tm1Tyj}/?$ $Mastr^{C57BL/6J}/?$	involves: 129S4/SvJae * C57BL/6J

tumorigenesis

malignant tumors (*J:92444*)

- astrocytoma susceptibility

Allelic Composition	Genetic Background
Mdm2^{tm1Glo}/Mdm2^{tm1Glo} Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	involves: 129S7/SvEvBrd * C57BL/6J

normal phenotype
no phenotype detected (*J:29810*)

Allelic Composition	Genetic Background
Trp53^{tm1Tyj}/Trp53^{tm1Tyj} Xrcc1^{tm1Rpe}/Xrcc1^{tm1Rpe}	involves: 129X1/SvJ

lethality/embryonic-perinatal
embryonic lethality during organogenesis (*J:54226*)
- death by E9.0 to E9.5, 12 to 24 hours after mice homozyg Xpre1^{tm1Rpe} alone

embryogenesis
reduced embryo size (*J:54226*)
- but bigger than mice homozygous for Xpre1^{tm1Rpe} alone

delayed embryonic development (*J:54226*)
- developmental arrest ~ 6 h after mice homozygous for Xp
- unlike mice homozygous for Xpre1^{tm1Rpe} alone, small amo mesoderm found

growth/size
reduced embryo size (*J:54226*)
- but bigger than mice homozygous for Xpre1^{tm1Rpe} alone

Allelic Composition	Genetic Background
Tg(Actb-NOTCH1)1Shn/0 Tg(Nes-cre)1Kln/0 Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	involves: C57BL/6J

lethality/embryonic-perinatal
embryonic lethality (*J:90392*)
- fewer than expected double transgenic homozygous mutar due to incomplete penetrance of Trp53^{tm1Tyj} embryonic le

cellular
cellular phenotype (*J:90392*)
- at E10 - 11.5 no increase in the number of apoptotic cells found unlike in double transgenics with wild-type Trp53

Allelic Composition	Genetic Background
Tg(Actb-NOTCH1)1Shn/0 Tg(Nes-cre)1Kln/0 Trp53^{tm1Tyj}/Trp53^{+}	involves: C57BL/6J

cellular
abnormal apoptosis (*J:90392*)
- at E10 - 11.5 the number of apoptotic cells in the brain is i

Allelic Composition	Genetic Background
Trp53^{tm1Tyj}/Trp53^{tm1Tyj} Xrcc4^{tm1Fwa}/Xrcc4^{tm1Fwa}	Not Specified

tumorigenesis
altered tumor susceptibility/resistance (*J:61973*)

Mouse models

Mouse models of human diseases involving Trp53^{tm1}

Human Disease	Note	Genotype	
		Allelic Composition	Genetic Backgrou
Models with phenotypic similarity to human diseases associated TP53.			
Li-Fraumeni Syndrome 1; LFS1 OMIM ID:151623		Trp53^{tm1Tyj}/Trp53^{+}	involves: 129S2/Sv
		Trp53^{tm1Tyj}/Trp53^{tm1Tyj}	involves: 129S2/Sv
		Trp53^{tm1Tyj}/Trp53$^{tm3.1Tyj}$	involves: 129S2/Sv * 129S4/Sv
		Trp53^{tm1Tyj}/Trp53$^{tm2.1Tyj}$	involves: 129S2/Sv * 129S4/Sv
		Trp53^{tm1Tyj}/Trp53^{+}	involves: 129S2/Sv * C57BL/
Models with phenotypic similarity to human diseases not asso human TP53.			
Neurofibromatosis, Type I; NF1 OMIM ID:162200	1	Nf1^{tm1Tyj}/Nf1^{+} Trp53^{tm1Tyj}/Trp53^{+}	involves: 129/Sv * C57BL/6

[1]NF1 is associated with this disease in humans.

Additional information

This mutant allele was produced by a targeted neo insertion into the Trp53 Homozygotes show no visible phenotype but develop tumors at 3-6 month Heterozygotes develop tumors at 10 months of age. These mice model sor features of human Li-Fraumeni syndrome (OMIM 151623), a form of famili with mutations in TRP53 (J:16022)(J:16023) A specific human mutation fo hepatocellular carcinomas caused by hepatitis B infection or by aflatoxin e been created in a mouse model, resulting in a similar gene product (J:273

References

(Original) J:17728 Jacks T *et al.*, "Tumor spectrum analysis in mice." Curr Biol 1994 Jan 1;4(1):1-7

All references(166)

JAX® Mice Data Sheet

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Strain Name: 129-*Trp53*^{tm1Tyj}/J
Stock Number: 002080

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View Pricing for International Destinations

General Terms and Conditions of Sale

Former Names 129-*Trp53*^{tm1Tyj} (Changed: 03-dec-2003)
129S1/SvImJ-*Trp53*^{tm1Tyj} (Changed: 11-mar-2001)

Strain Common Name 129S3/SvImJ-*Trp53*^{tm1Tyj};

Symbol ***Trp53***^{tm1Tyj};

Product Information
Strain Details

Type JAX® GEMM® Strain - Targeted Mutation;
Additional information on JAX® GEMM® Strains.

Investigator - Mutation Made By Dr. Tyler Jacks, Massachusetts Institute of Technology

Investigator - Donating Dr. Tyler Jacks, Massachusetts Institute of Technology

ES Cell Line D3 (129S2/SvPas)

Appearance white-bellied agouti
Related genotype A^w/A^w

Strain Description

Mice homozygous for the *Trp53*^{tm1Tyj} mutation show no visible phenotype but most develop tumors (principally lymphomas and osteosarcoma) at 3-6 months of age. Heterozygous mice develop tumors at about 10 months of age. These mice model some of the features of human Li-Fraumeni syndrome, a form of familial breast cancer with mutations in TRP53. Homozygous mice may produce a litter before succumbing to tumors.

Strain Development
The *Trp53^{tm1Tyj}* mutant strain was developed in the laboratory of Dr. Tyler Jacks at the Center for Cancer Research at the Massachusetts Institute of Technology. The 129-derived D3 ES cell line was used. The founder mouse was crossed to 129/Sv.

Gene Details

Symbol *Trp53^{tm1Tyj}*
Allele Name targeted mutation 1, Tyler Jacks
Gene Symbol and Name *Trp53*, transformation related protein 53
Chromosome 11
Gene Common Name(s) p53;
Symbol Description The *Trp53* gene encodes a tumor suppressor protein (p53) that is critical for maintenance of normal cellular function, arresting the cell cycle and promoting apoptosis. The MDM2 protein binds TRP53 (p53) keeping levels low and holding apoptosis in check. DNA damage induces phosphorylation of either p53 or MDM2. This prevents the two proteins from interacting, and results in the stabilization and acivation of p53. Mutations in the *Trp53* gene have been found in almost all human cancers with varying degrees of frequency. Mutation frequencies of up to 50-80% are found in human lung, colon, and breast cancer. Mutant TRP53 protein leads to uncontrolled cell growth and tumor development. Mouse Locus Catalog entry

Control Information

Symbol	Control
Trp53^{tm1Tyj}	Wildtype from the colony
Trp53^{tm1Tyj}	129S1/SvImJ 002448

Considerations for Choosing Controls
Control Pricing Information for JAX® GEMM® Strains

Genotyping Protocols

Trp53^{tm1Tyj}

Colony Maintenance

Breeding and Husbandry Expected coat color from breeding:White Bellied Agouti
Homozygous males MAY produce a litter, but will most likely only produce 1 litter.

Diet Information LabDiet® 5K52/5K67

Related Strains

Strains carrying *Trp53^{tm1Tyj}* allele:

002101 B6.129S2-*Trp53^{tm1Tyj}*/J
002103 B6;129S2-*Trp53^{tm1Tyj}*/J
002526 C.129S2(B6)-*Trp53^{tm1Tyj}*/J
002547 C3Ou.129S2(B6)-*Trp53^{tm1Tyj}*/J
002899 FVB.129S2(B6)-*Trp53^{tm1Tyj}*/J

Strains carrying other alleles of *Trp53* :

004301 129-*Trp53^{tm1Holl}*/J

Additional Web Information

Genetic Quality Control Annual Report
New 129 Nomenclature Bulletin

Research Applications

This mouse can be used to support research in many areas including:

Trp53^{tm1Tyj} related

Apoptosis Research
Endogenous Regulators

Cancer Research
Increased Tumor Incidence (Lymphomas)
Increased Tumor Incidence (Other Tissues/Organs: osteosarcoma)
Toxicology
Tumor Suppressor Genes

Immunology and Inflammation Research
Intracellular Signaling Molecules

Mouse/Human Gene Homologs
Li-Fraumeni syndrome

Research Tools
Toxicology Research (drug/compound testing)
Toxicology Research (B and T cell deficiency) (xenograft transplant host)

References

Primary Reference

Jacks T, Remington L, Williams BO, Schmitt EM, Halachmi S, Bronson RT, Weinberg RA. 1994. Tumor spectrum analysis in p53-mutant mice. Curr Biol 4 :1-7. [PubMed: 7922305]

Additional References

Price and Supply Information

Strain Name: **129-*Trp53*^{tm1Tyj}/J**

Stock Number: **002080**

Price Details

Prices are based on shipping destination. To view prices, select your shipping destination.

- USA, Canada or Mexico
- International Destinations (EXCEPT Canada and Mexico)

Supply Details

Standard Supply	**Repository-Cryopreserved.** Please refer to the Supply Notes for further information.
Supply Notes	This strain is included in the Induced Mutant Resource collection. **Cryorecovery - Standard** The recovery process begins when a signed agreement form is returned to the Customer Service Department after order placement. Although results vary by strain, at least two males and two females (two pairs) will be provided, typically within 15 weeks of our receipt of the signed agreement form. If the first recovery attempt is unsuccessful or only one pair is recovered, a second recovery will be done, extending the delivery time to approximately 25 weeks. At least one member of each pair will be of known genotype and will carry the mutation if it is a mutant strain. Note that pairs may not reflect the mating scheme utilized by The Jackson Laboratory prior to cryopreservation of the strain. Mating schemes are sometimes modified for successful cryopreservation. Price represents a repository maintenance fee, which includes the cost of recovery of the strain from the cryopreservation resource and the periodic replacement of the frozen embryos used for recovery. **Cryorecovery to establish a Dedicated Supply for greater quantities of mice** One to two pairs will be recovered to establish a Dedicated Supply of mice. Price by quotation. For more information on Dedicated Supply, please contact JAX® Services: Tel: 800.422.MICE (6423) or 207.288.5845; Email: jaxservices@jax.org.
Licensing	See **General Terms and Conditions of Sale** below for Licensing and Use Restrictions.
Control Information	View Control Information in Strain Details. View Control Pricing Information for JAX® GEMM® Strains.

General Terms and Conditions of Sale

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OncoMouse™ requires a license from DuPont, see Licenses for Strains with OncoMouse™ Technology.
P53 Mice are subject to U.S. 5,569,824 and corresponding license requirements.

The Jackson Laboratory's Genotype Promise

The Jackson Laboratory has rigorous genetic quality control and mutant gene genotyping programs to ensure the genetic background of JAX® Mice strains as well as the genotypes of strains with identified molecular mutations. JAX® Mice strains are only made available to researchers after meeting our standards. However, the phenotype of each strain may not be fully characterized and/or captured in the strain data sheets. **Therefore, we cannot guarantee a strain's phenotype will meet all expectations.** To ensure that JAX® Mice will meet the needs of individual research projects or when requesting a strain that is new to your research, we suggest ordering and performing tests on a small number of mice to determine suitability for your particular project.

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JAX|Bulletin

Number 1
June 1999; Revised Jun

New 129 Nomenclature - revised

A large degree of genetic diversity among 129 substrains was recently identifi at The Jackson Laboratory (Simpson *et al.*, *Nat Genetics* 16:19-27, 1997), an by investigators at Case Western Reserve University (Threadgill *et al.*, *Mamm* 393, 1997). Because of the importance of 129 mice in creating "knockout" an mutant mice, the *International Committee on Standardized Genetic Nomencla* introduced a new nomenclature to distinguish different 129 parental lines and strains.

The overall result is a change in 129 nomenclature that specifies groups of str their common parental lineage. The major parental lineages include:

- 129 strains derived from the original parent strain (designated by the le
- 129 strains derived from a congenic strain made by outcrossing to intrc mutation (designated by the letter S)
- 129 strains derived from the 129 congenic that originally carried the te (designated by the letter T).

The numbers following the letters (*e.g.*, P3) distinguish the different 129 pare each lineage.

These nomenclature changes affect the strain names for inbred 129 mice and transgenes, or spontaneous or targeted mutations on a 129 background. The Laboratory has updated the 129 strain names for relevant JAX® Mice in the *1 and Product Guide*, and subsequent JAX® Mice catalogs, which also list forme for your convenience.

Many targeted mutations (*e.g.*, "knockouts") are maintained on a mixture of (particular 129 strain. This mixed genetic background was previously designate and subsequently B6;129. Strain names have been revised, *e.g.*, B6;129P or distinguishing between 129 strains of the parental (P) or steel (S) lineages.

The exact origin and breeding history of some spontaneous and targeted mut maintained on either a 129 background or mixed B6;129 is unknown. Therefo information has been eliminated from some strain names, and they are desigr or B6;129.

A copy of the article by Festing, *et al.* (*Mammalian Genome*, 10:836, 1999) fu the rationale behind the nomencla-ture changes and the revised nomenclature is found below.

If you have any questions regarding this change, contact Jackson Laboratory Support at tel: 800 422-MICE(6423) or 207 288-6423; fax: 207 288-6150.

Revised Nomenclature for Strain 129 Mice

Michael FW Festing (1), Elizabeth M Simpson (2), Muriel T Davisson (2), Larry
(2).

1. *MRC Toxicology Unit, University of Leicester, PO Box 138, Leicester LE1*
2. *The Jackson Laboratory, Bar Harbor, Maine, USA.*

Need for revised nomenclature

Two recent papers (Simpson *et al.*, 1997; Threadgill *et al.*, 1997) have shown substantial genetic variation among substrains of this important inbred strain. has apparently arisen as a result of genetic contamination, and the rest appea residual heterozygosity and/or "contaminant" alleles introduced during variou programs such as in the production of congenic strains carrying steel and susc teratomas.

Correct identification and designation of substrains is essential if the genotype strain is to be matched accurately with an appropriate embryonic stem cell lin development of "knockout" strains. Unfortunately, current nomenclature mak Thus substrains 129/SvJ and 129/SvJae are very different, but this is not imm even to someone with a good understanding of nomenclature rules. Moreover, substrains can only be accurately identified using nomenclature involving quit symbols. Thus, in view of the widespread use of these strains by people with l understanding of genetic nomenclature, it seems sensible to introduce new, si nomenclature which will minimise future misunderstandings particularly as inv sometimes referred to different substrains as simply "129", adding further cor

The new nomenclature

The following new nomenclature has been approved by the Committee on Sta Genetic Nomenclature for Mice. The aim is to provide short symbols that distir substrains when they are abbreviated from the frequently long and complicate symbols, either in common usage or in manuscripts. The new nomenclature is substrains identified and defined in terms of microsatellite markers by Simpso A letter and a number have been introduced in front of the slash that will une identify each of the substrains. The letter is either P, S, T or X indicating whet "Parental", "Steel", "Ter" (*i.e.* susceptible to teratomas) or a genetically-conta substrain [See *JAX® Notes* No. 481, Feb. 2001], respectively. A number will b differentiate between substrains within each grouping, working from left to rig Simpson *et al.* , (1997). All existing substrain symbols and gene symbols will only change is the introduction of a letter and a number in front of the slash. congenic strain such as 129/ReJ-*Lama2 dy* will take the strain designation of i will be designated 129P1/ReJ-*Lama2 dy*. This nomenclature change is equival to distinguish between RIII and RIIIS, where the latter differs substantially fr Table 1 shows the approved new nomenclature for each substrain. Note that 1 (000094), which exists as frozen embryos and has been discovered to be hete many loci, has not been included on this list as it is clearly not an inbred strai (002065) and 129/SvEms (002064) are presumed to be genetically identical. (002448) was derived from 000090, 129S1/Sv-+*p* + *Tyr-c Kitl Sl-J*/+ (former see *JAX® Notes* No. 481, Feb. 2001) in 1995 by selectively breeding out the s mutation. Therefore, except for the region surrounding *Kitl* on Chr 10, these t genetically identical. Designated 129S3/SvImJ in 1999 (Festing *et al.* 1999), renamed in February, 2001 to emphasize its relationship to 129S1/Sv-+*p* + *T*

Implementation

These new nomenclature rules should be put into effect as soon as possible, t recognised that this may take some time if it involves printing new literature,

References

[Festing MFW. Inbred strains of mice. Mouse Genome Informatics, The Jackso Bar Harbor, Maine. World Wide Web (URL: http://www.informatics.jax.org/). (

Simpson E. M., Linder C. C., Sargent E. E., Davisson M. T., Mobraaten L. E., a (1997) Genetic variation among 129 substrains and its importance for targete in mice. *Nature Genet.* 16, 19-27.

Threadgill D. W., Yee D., Matin A., Nadeau J. H., and Magnuson T. (1997) Ger 129 inbred strains: 129/SvJ is a contaminated inbred strain. *Mamm. Genome*

Note: Material in [ ] was added after publication

Table 1. New nomenclature for strain 129 mice [modified to incorporate 129S change]

Abbreviated designation	**Full designation**	**Former designation**
129P1-*Lama2*^{dy}	129P1/ReJ-*Lama2*^{dy}	129/ReJ-*Lama2*^{dy}
129P1	129P1/ReJ	129/ReJ
129P2	129P2/OlaHsd	129/OlaHsd
129P3	129P3/J	129/J
129X1	129X1/SvJ	129/SvJ
129S1	129S1/Sv-+^{p}+$^{Tyr\text{-}c}$*Kit*$^{Sl\text{-}J}$/+	129/Sv-+^{p}+$^{Tyr\text{-}c}$+*Mgf*$^{Sl\text{-}J}$/+
129S1	129S1/SvImJ	129S3/SvImJ (formerly 129/SvImJ, 129/Sv-+^{p}+$^{Tyr\text{-}c}$+$^{Mgf\text{-}Sl}$/J)
129S2	129S2/SvPas	129/SvPas
129S4	129S4/SvJae	129/SvJae
129S5	129S5/SvEvBrd	129/SvEvBrd
129S6	129S6/SvEvTac	129/SvEvTac
129S7	129S7/SvEvBrd-*Hprt*$^{b\text{-}m2}$	129/SvEvBrd-*Hprt*$^{b\text{-}m2}$
129S8	129S8/SvEv@J-*Gpi1*^{c} *Hprt*$^{b\text{-}m2}$	129/SvEv-*Gpi1*^{c} *Hprt*$^{b\text{-}m2}$ @J (forme 129/SvEv -*Hprt*$^{b\text{-}m2}$)
129T1	129T1/Sv-+^{p} *Tyr*$^{c\text{-}ch}$ *Ter*/+@Na	129/Sv-+^{p} *Tyr*$^{c\text{-}ch}$ *Ter*/+@Na
129T2	129T2/SvEms	129/SvEms (formerly 129/SvEms-+^{Ter}?)
129T2	129T2/SvEmsJ	129/SvEmsJ (formerly 129/SvEms-+^{Ter}?/J)

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Animal Model

Development of Spontaneous Mammary Tumors in BALB/c *p53* Heterozygous Mice

A Model for Li-Fraumeni Syndrome

Charlotte Kuperwasser,*† Gregory D. Hurlbut,† Frances S. Kittrell,‡ Ellen S. Dickinson,† Rudy Laucirica,§ Daniel Medina,‡ Stephen P. Naber,¶ and D. Joseph Jerry*†

From the Program in Molecular and Cellular Biology and the Department of Veterinary and Animal Sciences,† University of Massachusetts, Amherst, Massachusetts; the Departments of Cell Biology‡ and Pathology,§ Baylor College of Medicine, Houston, Texas; and the Department of Pathology,¶ Baystate Medical Center, Springfield, Massachusetts*

Breast cancer is the most frequent tumor type among women in the United States and in individuals with Li-Fraumeni syndrome. The *p53* tumor suppressor gene is altered in a large proportion of both spontaneous breast malignancies and Li-Fraumeni breast cancers. This suggests that loss of *p53* can accelerate breast tumorigenesis, yet *p53*-deficient mice rarely develop mammary tumors. To evaluate the effect of *p53* loss on mammary tumor formation, the $p53^{null}$ allele was back-crossed onto the BALB/c genetic background. Median survival was 15.4 weeks for BALB/c-$p53^{-/-}$ mice compared to 54 weeks for BALB/c-$p53^{+/-}$ mice. Sarcomas and lymphomas were the most frequent tumor types in BALB/c-$p53^{-/-}$ mice, whereas 55% of the female BALB/c-$p53^{+/-}$ mice developed mammary carcinomas. The mammary tumors were highly aneuploid, frequently lost the remaining wild-type *p53* allele, but rarely lost *BRCA1*. Although mammary tumors were rarely detected in BALB/c-$p53^{-/-}$ female mice, when glands from BALB/c-$p53^{-/-}$ mice were transplanted into wild-type BALB/c hosts, 75% developed mammary tumors. The high rate of mammary tumor development in the BALB/c background, but not C57Bl/6 or 129/Sv, suggests a genetic predisposition toward mammary tumorigenesis. Therefore, the BALB/c-$p53^{+/-}$ mice provide a unique model for the study of breast cancer in Li-Fraumeni syndrome. These results demonstrate the critical role that the *p53* tumor suppressor gene plays in preventing tumorigenesis in the mammary gland. ***(Am J Pathol 2000, 157:2151–2159)***

The p53 tumor suppressor gene plays a complex and critical role in maintaining genome integrity. In cells with damaged DNA, p53 mediates the decision to arrest cells to allow for DNA repair or eliminate the cell by apoptotic pathways. Mutations in the p53 tumor suppressor gene (*TP53*) are the most common genetic abnormality being found in >50% of all human cancers, emphasizing the importance of p53 function for suppression of tumors.[1] Germline mutations in the p53 tumor suppressor gene are associated with Li-Fraumeni syndrome in which early-onset breast cancer is the most common cancer affecting women with Li-Fraumeni syndrome.[2–4] Although this suggests that the loss of *p53* is a critical event in the progression of breast tumorigenesis, *p53*-deficient mice rarely developed mammary tumors.[5] Instead, mice lacking *p53* died prematurely from a variety of other tumors.[6] The lack of mammary tumor formation in mice deficient for *p53* suggested that loss of *p53* alone was not sufficient for tumor development in the mammary gland or that its role as a tumor suppressor in this tissue was not essential.

Different strains of inbred mice have been shown to differ in their susceptibility to mammary tumorigenesis.[7] Female BALB/c mice were shown to be sensitive to radiation-induced mammary tumor development, whereas C57Bl/6 mice were resistant.[7,8] This difference was correlated with an increase in chromosomal instability in

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BALB/c mice compared to the C57Bl/6 mice rather than variations in hormonal levels.[7] In the analysis of families with Li-Fraumeni syndrome, it was shown that some women, in particular families, developed breast cancers more frequently than women in other families,[9] suggesting the presence of modifier loci that may also be involved in the predisposition to mammary tumor formation. Similarly, lack of mammary tumorigenesis in *p53*-deficient mice could have been because of the resistance of the genetic backgrounds.

Therefore, the $p53^{null}$ allele was transferred to the BALB/c genetic background to determine whether this altered the tumor spectrum. BALB/c-$p53^{-/-}$ mice displayed a similar tumor incidence and spectrum to that observed in other backgrounds with a predominance of lymphomas and hemangiosarcomas. An abnormal mammary phenotype, ranging from stromal alterations to preneoplastic changes in the mammary epithelium, was observed in the majority of the female BALB/c-$p53^{-/-}$ mice. In contrast, female BALB/c-$p53^{+/-}$ mice showed a prevalence of mammary carcinomas with a latency of 8 to 14 months. These data reveal a genetic predisposition to mammary tumor development in BALB/c mice, which is accelerated upon loss of *p53*. Furthermore, the prevalence of mammary tumors in BALB/c-$p53^{+/-}$ mice provides a model that more accurately reflects the tumor spectrum in individuals with Li-Fraumeni syndrome.

Materials and Methods

Mice and Tissues

C57Bl/6x129/Sv *p53*-deficient mice (generous gift from Tyler Jacks, Cambridge, MA) were mated with BALB/c mice. The $p53^{null}$ allele from these mice was backcrossed for nine generations onto the BALB/cMed strain. Individuals were genotyped by multiplexed PCR as described previously.[10,11] Mice were monitored weekly for 18 months and sacrificed when overt tumor development was detected or when signs of morbidity were evident. A total of 44 BALB/c-$p53^{-/-}$ mice (eight male, 36 female) and 45 BALB/c-$p53^{+/-}$ mice (seven male, 38 female) underwent necropsy. Five wild-type mice were sampled from age-matched animals in our colony (n = 50). Tumor tissues as well as the fourth inguinal mammary glands were excised and fixed for 8 to 12 hours in 10% neutral-buffered formalin. Tissues were stored in 70% ethanol before embedding in paraffin. Tissues were sectioned at a thickness of 4 μm and were stained with hematoxylin and eosin for evaluation by light microscopy. Additional samples of tumor tissue were snap-frozen and stored in liquid nitrogen.

Ploidy Analysis

Single cell suspensions were obtained by digesting five 50-μm paraffin sections in pepsin. The suspensions were filtered, stained with propidium iodide, and analyzed using a FACScan flow cytometer. A total of 20,000 events were collected from each sample as described previously.[12] DNA histograms were produced using ModFit LT software (Verity Software House, Topsham, ME).

Cytogenetic Analysis

Fresh tumor tissue was removed at necropsy, rinsed with Dulbecco's modified Eagle's medium (Life Technologies, Inc., Grand Island, NY) to remove cellular debris, minced, and digested for 3 hours in 10 μg/ml of collagenase III (Sigma, St. Louis, MO). The cell suspension was washed with 5% adult bovine serum in phosphate-buffered saline and cultured in a 100-mm dish in Dulbecco's modified Eagle's medium/F12 media supplemented with sodium bicarbonate, HEPES buffer, 2% adult bovine serum, insulin (10 μg/ml), and epidermal growth factor (5 ng/ml) until 60% confluent. The actively dividing culture was treated with colcemid (Life Technologies, Inc.) for 18 hours, then harvested by trypsin digestion. Cells were lysed with 0.068 mol/L KCl and fixed with a 3:1 methanol and glacial acetic acid solution. Interphase and metaphase nuclei were trypsinized and stained with Giemsa (BDH Chemicals, Poole, UK) for visualization.

Southern Blot Analysis

Fresh-frozen tumor samples taken at the time of necropsy were homogenized in 100 mmol/L Tris, 5 mmol/L ethylenediaminetetraacetic acid, 0.2% sodium dodecyl sulfate, 200 mmol/L NaCl, and digested with 100 μg/ml proteinase K. Genomic DNA was extracted and purified with phenol/chloroform (1:1; v/v). Ten micrograms of DNA were digested with *Eco*RI and *Stu*I, then separated on a 0.7% agarose gel. The DNA was transferred to a nylon membrane, then hybridized to a genomic clone (probe B, a generous gift from Tyler Jacks) spanning the region from exon 7 to exon 9 of the *p53* gene.[11] The blot was stripped and hybridized sequentially with probes for *BRCA1* (exon 11, provided by Roger Wiseman, Research Triangle Park, Durham, NC), and *β-casein* cDNA (exons 1 to 9). Southern blot was performed in duplicate and quantitation was performed using a phosphorimager (Molecular Dynamics, Sunnyvale, CA). Hybridization values for *p53* and *BRCA1* were normalized to *β-casein* to control for loading variation. Hybridization values were compared to the genomic DNA of corresponding genotypes isolated from tail biopsies. Allelic loss was scored if the hybridization value of the tumor was less than or equal to 50% of the value obtained from $p53^{+/-}$ tail DNA.

Mammary Transplants

Whole gland transplants were performed by surgically removing the fourth inguinal mammary glands from mature (>8weeks) BALB/c-$p53^{-/-}$ (n = 16) or BALB/c-$p53^{+/+}$ (n = 8) females and suturing them onto the abdominal fascia of age-matched BALB/c wild-type recipients. Reconstituted mammary gland transplants were prepared with modifications of previous procedures.[13] The fourth inguinal mammary glands from 21- to 24-day-old BALB/c-$p53^{+/+}$ females were cleared of

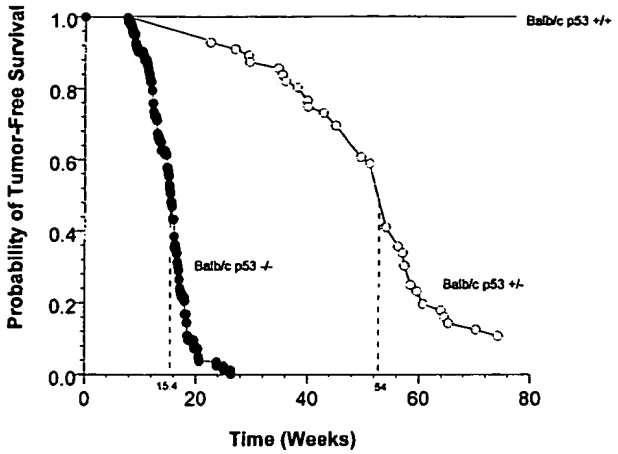

Figure 1. Survival curves of BALB/c *p53*-deficient mice. The probability of tumor-free survival of BALB/c-*p53*$^{-/-}$ mice (n = 85; **closed circles**), and BALB/c-*p53*$^{+/-}$ mice (n = 56; **open circles**) was monitored for 80 weeks. No wild-type animals died during this study (n = 5). **Dashed lines** represent the median time at which 50% of the animals had developed tumors.

mammary epithelium. Single ducts from mature BALB/c-*p53*$^{-/-}$ donors were dissected and transplanted into the cleared fat pads from BALB/c-*p53*$^{+/+}$ recipients (n = 14). Two weeks after the initial surgery, the reconstituted glands were removed and then transplanted onto the abdominal fascia of age matched BALB/c wild-type females. All transplant recipients were palpated weekly for tumor formation and sacrificed when tumor masses were detected. Tissues were processed and sectioned for histological evaluation as above.

Results

Tumor Incidence and Survival Rate of BALB/c-p53-Deficient Mice

Mice deficient for *p53* showed heightened tumor susceptibility compared to wild-type animals. BALB/c-*p53*$^{-/-}$ mice developed tumors earlier and at higher frequency than did BALB/c-*p53*$^{+/-}$ mice. All of the BALB/c-*p53*$^{-/-}$ mice had developed tumors or died by 26 weeks of age with a median of 15.4 weeks (Figure 1). Among the BALB/c-*p53*$^{+/-}$ mice, 50% developed tumors by 54 weeks and only 10% of the animals were tumor-free throughout the duration of the study. No wild-type animals developed tumors within the 80-week period of observation.

Tumor Spectrum and Mammary Phenotype in BALB/c- p53$^{-/-}$ Mice

There were four predominant cancers detected in BALB/c-*p53*$^{-/-}$ mice (Figure 2A). Multiple tumor types were often present in individual mice. Lymphomas were the most frequent tumor type, affecting 53% of the BALB/c-*p53*$^{-/-}$ mice and involved primarily the thymus, lymph nodes, or other secondary lymphoid tissues. Hemangiosarcomas were the second most frequently detected tumor, affecting 39% of the animals. These tumors usually were present in the subcutaneous and soft tissues on the limbs or head, or in the mammary glands. Although the focus of the study was on primary tumors, metastases were detected in the lung and liver in several cases. Only one mammary carcinoma developed in the BALB/c-*p53*$^{-/-}$ mice.

Previous studies have shown that mating of *p53* heterozygous animals yielded a reduced number of *p53*-null female offspring because of exencephaly.[14] Similarly, BALB/c-*p53*$^{-/-}$ female offspring were not born at the expected Mendelian ratios indicating that there were gestational defects resulting in embryonic lethality. BALB/c-*p53*$^{-/-}$ females were primarily normal, but microscopic lesions were detected in 78% of the mammary glands. These included sarcomas, epithelial hyperplasia at 2 to 5 months of age, and alterations in stromal morphology. Stromal abnormalities and sarcomas were the predominant mammary lesions present in 68% of the BALB/c-*p53*$^{-/-}$ female mice. The stromal changes were characterized by adipocytes with microvesicular fat droplets and a hypercellularity of the stroma (Figure 2C, ii). Periductal stromal tissue was thickened and many of the mammary ducts were markedly dilated with attenuated epithelial lining (Figure 2C, iii). In addition to the morphological changes observed in the mammary glands of nulliparous BALB/c-*p53*$^{-/-}$ mice, abnormal stromal and glandular architecture were also seen in glands of pregnant, lactating, and postinvoluting mice (data not shown).

Tumor Spectrum and Mammary Phenotype in BALB/c-p53 Heterozygous Mice

Although BALB/c-*p53*$^{+/-}$ mice developed tumors frequently, there was a delay in their appearance and a difference in the tumor spectrum compared to the BALB/c-*p53*$^{-/-}$ mice. Hemangiosarcomas, lymphomas, and osteosarcomas commonly found in some other strains of *p53*-heterozygous mice[6,11] were less frequent in BALB/c-*p53*$^{+/-}$ mice, but still accounted for 36% of all of the tumors (Figure 3A).

Although mammary carcinomas were rare in BALB/c-*p53*$^{-/-}$ mice, they were the most prevalent tumor type in BALB/c-*p53*$^{+/-}$ mice, accounting for 42% of the tumors (Figure 3A). All of the female heterozygous mice developed mammary abnormalities, which were either overt mammary carcinomas (55%) or hyperplasias (45%) (Figure 3B). Mammary tumors originated in both the inguinal and thoracic glands with a latency of 8 to 14 months. These tumors were generally adenoacanthomas or acinar-type adenocarcinomas (Figure 3C) with occasional poorly differentiated carcinomas identified. One animal developed two separate primary mammary tumors in different glands that were of different histological types. Many of the mammary carcinomas had infiltrating growth patterns, however metastases were not detected. Mammary carcinomas were present in nulliparous animals

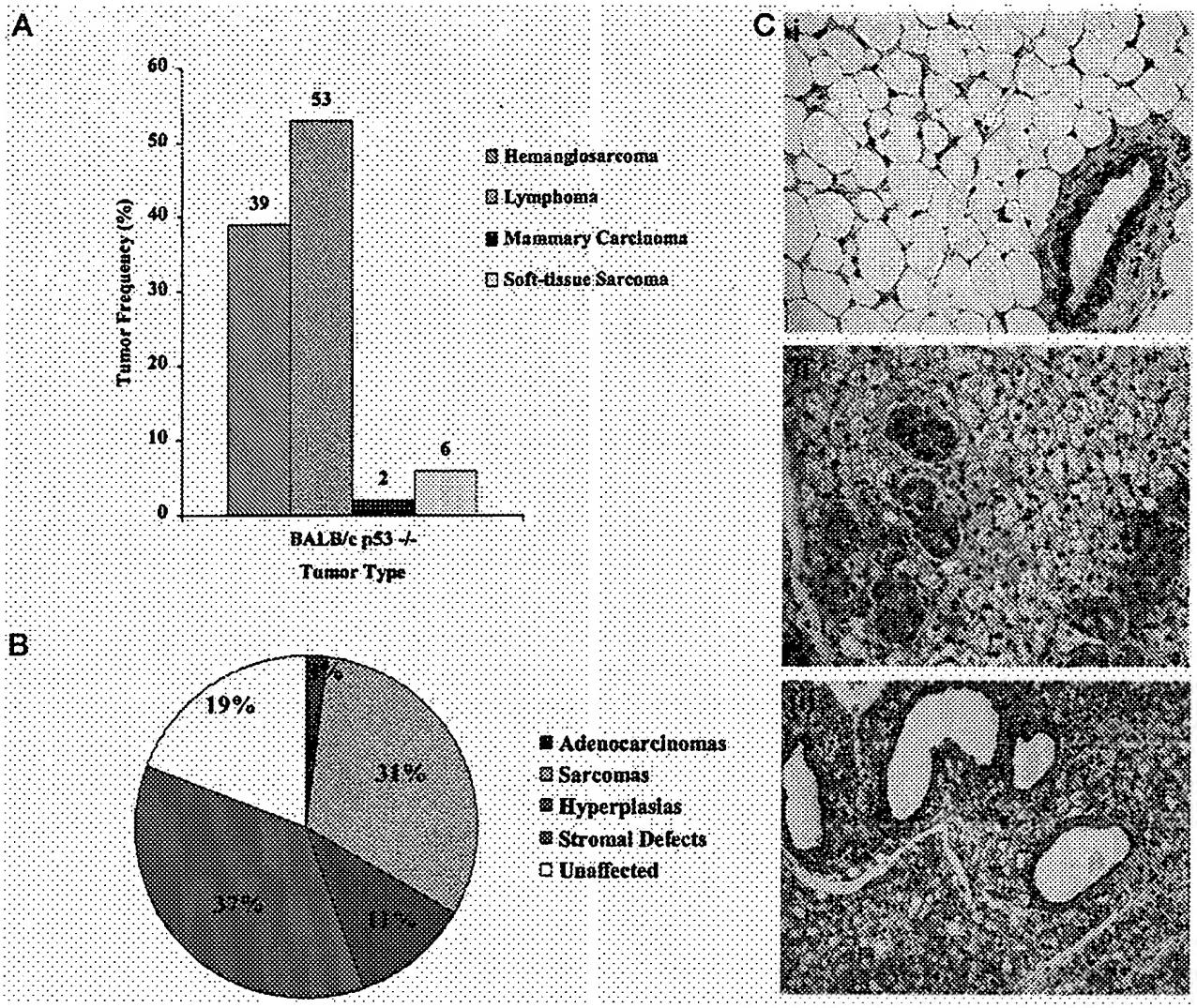

Figure 2. Tumor distribution and mammary abnormalities in BALB/c-*p53* $^{-/-}$ mice. **A:** Tumor spectrum from BALB/c-*p53* $^{-/-}$ mice. Frequency histogram of tumor types observed in both male and female mice ($n = 44$). **B:** Mammary phenotype of female BALB/c-*p53* $^{-/-}$ mice. Relative frequency of abnormalities detected in the inguinal or thoracic gland from nulliparous and breeder females ($n = 36$). **C:** H&E-stained sections of mammary tissue from BALB/c-*p53* $^{-/-}$ females. The normal murine mammary gland architecture is characterized by large adipocytes in the stroma surrounding a sparse population of ducts (**i**, ×40 objective). Typical stromal changes observed in BALB/c-*p53* $^{-/-}$ females (**ii** and **iii**). Stroma characterized by microvesicular adipocytes and proliferation of mammary ducts (**ii**, ×40 objective). Hypercellular stroma and dilated ducts with attenuation of the mammary epithelium (**iii**, ×20 objective).

and breeder females. Epithelial hyperplasia was detected in all of the female BALB/c-*p53*$^{+/-}$ mice that did not develop mammary tumors (Figure 3C, iv) and was also present in the ductal epithelium of those mice that developed mammary carcinomas.

Frequent Loss of p53 but Not BRCA1 in Mammary Tumors from BALB/c-p53$^{+/-}$ *Mice*

Flow cytometry was performed to determine whether the tumors contained a population of aneuploid cells (Figure 4A). Seventy-one percent (10 of 14) of the mammary tumors analyzed exhibited rates of aneuploidy ranging from 17 to 89%. Tumors that maintained a diploid state had relatively high S-phase fractions ranging from 5 to 21%. Cytogenetic analysis was performed to examine the types of chromosomal abnormalities present in these tumors (Figure 4B). Chromosomal translocations, strand breaks, and aberrant mitotic exchanges were common abnormalities associated with mammary tumors from BALB/c-*p53*$^{+/-}$ mice.

Because of the high degree of aneuploidy and chromosomal abnormalities detected in the mammary tumors, Southern blot analysis was performed on mammary carcinomas to analyze the status of the wild-type *p53* allele in the BALB/c-*p53*$^{+/-}$ mice (Figure 4C). In all seven of the mammary tumors analyzed, there was partial or complete loss of the wild-type allele. In contrast, the wild-type *p53* allele was retained in a prepucial adenoma and a salivary gland carcinoma from BALB/c-*p53*$^{+/-}$ mice. Tail DNA wild-type, *p53*$^{+/-}$, and *p53*$^{-/-}$ animals were used as positive controls for DNA levels. There was no correlation between ploidy status of the mammary carcinoma and loss of heterozygosity.

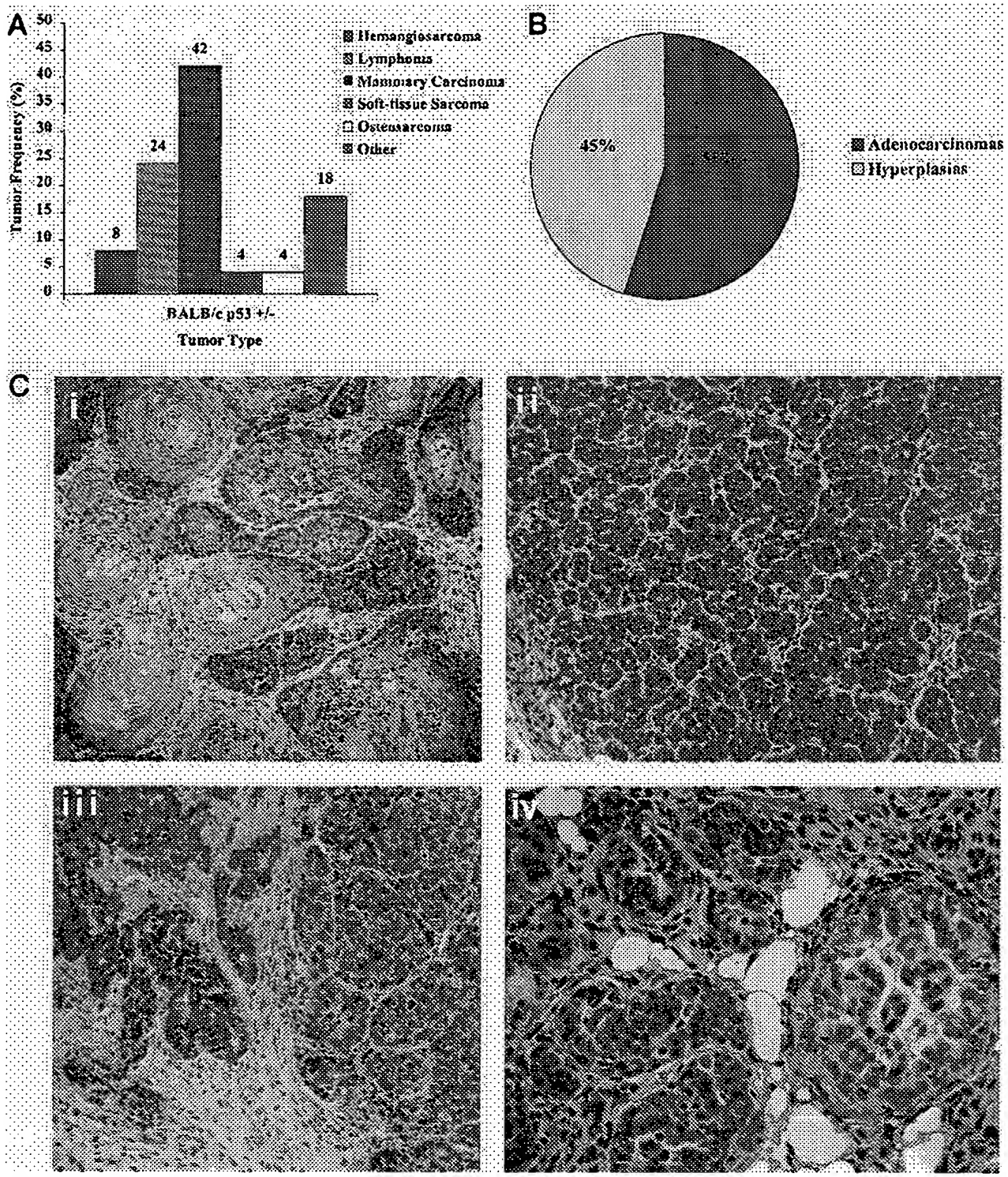

Figure 3. Tumor distribution and mammary abnormalities in BALB/c-*p53*$^{-/-}$ mice. **A:** Tumor spectrum from BALB/c-*p53*$^{-/-}$ mice. Frequency histogram of tumor types observed in both male and female mice (n = 45). **B:** Mammary phenotype of female BALB/c-*p53*$^{-/-}$ mice. Relative frequency of abnormalities detected in the inguinal or thoracic mammary glands from nulliparous and breeder females (n = 38). Mammary hyperplasia was observed either alone or in association with tumors in all glands analyzed. **C:** H&E-stained sections of mammary tumor tissue from BALB/c-*p53*$^{-/-}$ females (×20 objective). A typical adenoacanthoma characterized by keratin formation (**i**) and an adenocarcinoma with small acinar structures (**ii**). H&E section of a mammary carcinoma infiltrating adjacent stroma. (**iii,** ×20 objective). Ductal hyperplasia commonly seen in BALB/c-*p53*$^{-/-}$ female mice (**iv,** ×40 objective).

Because the genes for *BRCA1* and *p53* lie 21 centimorgans apart on chromosome 11 in mice, it was possible that *BRCA1* may also have been lost in the in the mammary tumors of BALB/c-*p53*$^{+/-}$ mice. Therefore, Southern blot analysis for *BRCA1* was performed on those mammary carcinomas that were analyzed for *p53* loss of heterozygosity (Figure 4C, bottom). In all of the mammary tumors analyzed, little or no loss of *BRCA1* was

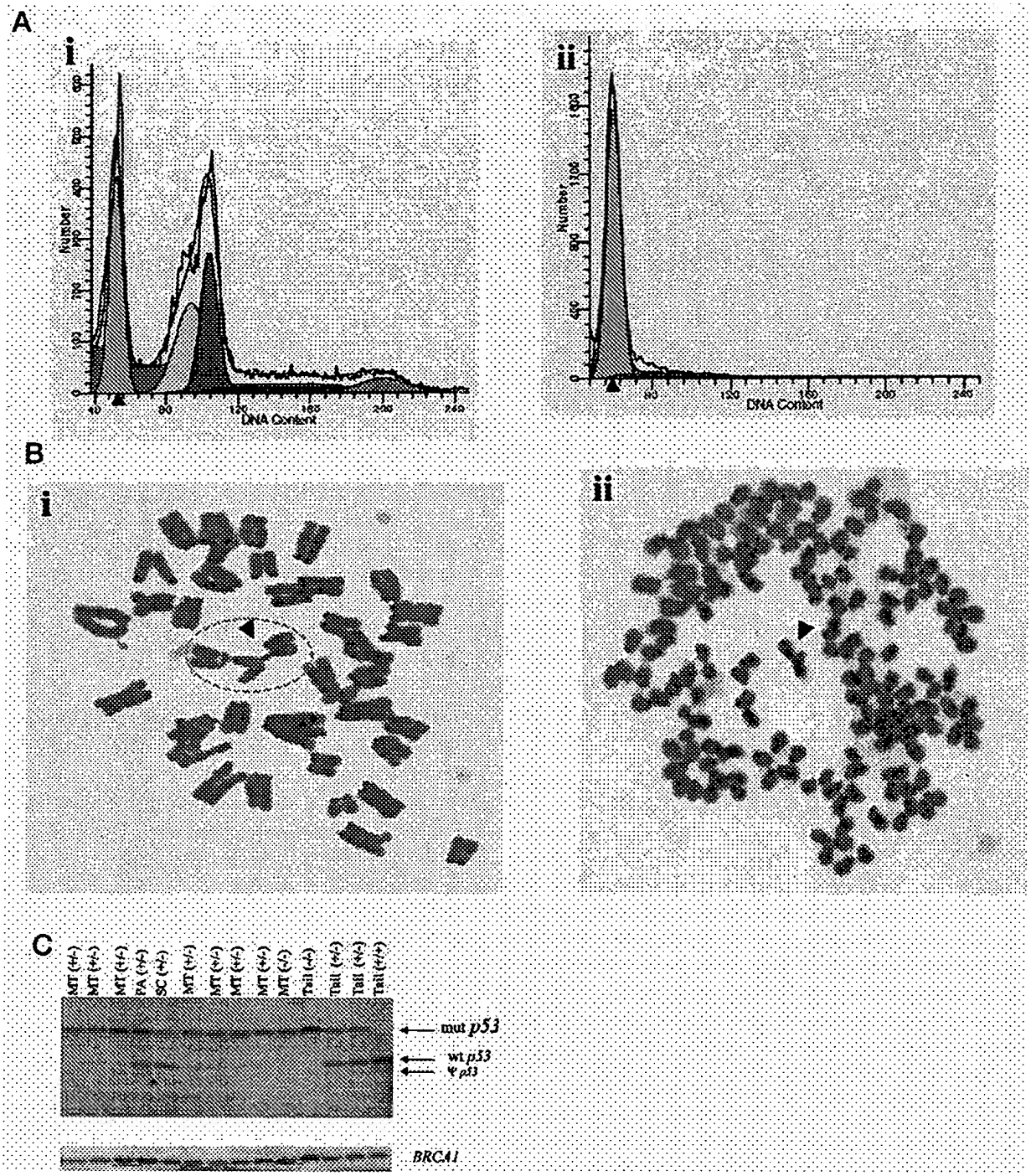

Figure 4. Analysis of DNA from BALB/c-*p53*$^{-/-}$ mammary carcinomas. **A:** Representative DNA histograms determined by FACS analysis from mammary tumors (n = 14). Seventy-one percent of the tumors were aneuploid with DNA content >40 (**i**), and the remaining 29% of the tumor were diploid (**ii**). The solid line represents the distribution of cells. Subpopulations of cells were calculated using the ModFit LT software and are represented by the shaded peaks. **B:** Representative Geimsa-stained (original magnification, ×100) metaphase spreads of mammary carcinomas from BALB/c-*p53*$^{-/-}$ females. Typical abnormalities such as quadriradial chromosomes (**i**) and chromosome breaks commonly found in aneuploid karyotypes (**ii**) marked by **arrows**, respectively. **C:** Southern blot analysis of *p53* and *BRCA1* in BALB/c-*p53*$^{-/-}$ mammary tumors. Genomic DNA from mammary tumors (MT), a prepucial adenoma (PA), a salivary gland carcinoma (SC), and tails (tail) were digested with *Eco*RI and *Stu*I. Loss of heterozygosity was determined using a genomic DNA clone spanning exon 7 to exon 9 of the *p53* gene. Three bands were detected in tail DNAs from BALB/c-*p53*$^{-/-}$ mice (tail +/−). These fragments represent the wild-type allele (wt *p53*), the mutant allele (mut *p53*), and the pseudogene (ψ *p53*). The blot was reprobed with exon 11 of *BRCA1* to determine whether there was loss of *BRCA1* in the mammary tumors from BALB/c-*p53*$^{-/-}$ mammary tumors.

detected compared to tail DNA. The β-casein locus was also analyzed to control for the possibility of random losses because of chromosomal instability. Similar to the *BRCA1* locus, there was no evidence of significant loss of alleles at the β-casein locus compared to tail DNA (data not shown). Therefore, preferential loss of the wild-type *p53* allele in these mammary tumors was not a random event, but seems to be selected for during tumor progression.

Table 1. Tumor Incidence in BALB/c-p53$^{-/-}$ Mammary Gland Transplants

Transplant genotype	*n*	Accepted (%)	Tumors (%)
Whole-gland transplants*			
+/+ whole gland	8	8 (100)	0 (0)
−/− whole gland	16	12 (75)	9 (75)
Reconstituted gland transplants†			
$p53^{null/wt}$†	14	11 (79)	6 (55)
$p53^{wt/wt}$‡	4	100	0 (0)

*Whole glands and reconstituted glands were transplanted into BALB/c wild-type recipients.
†$p53^{-/-}$epithelium was transplanted into wild-type stroma.
‡Wild-type epithelium transplanted into wild-type stroma.

Development of Mammary Tumors from BALB/c-p53$^{-/-}$ Epithelium

Because mammary tumors developed in only one of the BALB/c-$p53^{-/-}$ mice, it was possible that early mortality masked the development of mammary carcinomas. Therefore, whole glands from BALB/c-$p53^{-/-}$ mice were transplanted into wild-type (BALB/c-$p53^{+/+}$) recipients and monitored for tumor formation. Of the whole gland transplants that were accepted, 75% developed mammary carcinomas (Table 1), which were first observed by 7 months after transplantation (Figure 5A). Several BALB/c-$p53^{-/-}$ whole gland transplants failed to engraft in the BALB/c wild-type recipients (25%). No tumors developed in the whole gland transplants derived from wild-type BALB/c mice.

Morphological changes in the mammary stroma were observed frequently in BALB/c-$p53^{-/-}$ mice. To deter-

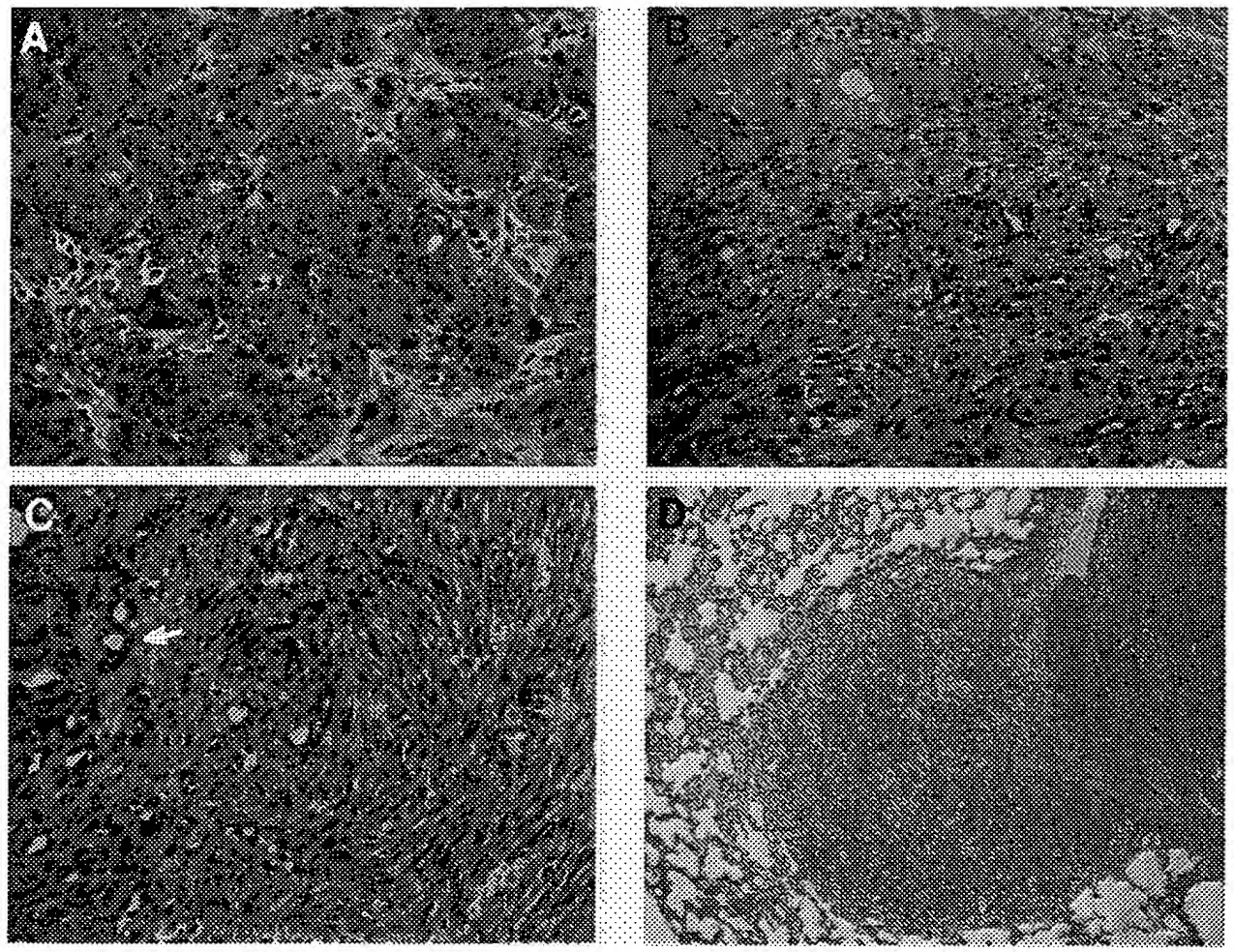

Figure 5. Histology of mammary carcinomas derived from transplants. **A:** The transplantation of a BALB/c-$p53^{-/-}$ whole gland into a wild-type recipient yielded mammary tumors as early as 7 months. Typical adenocarcinoma with structures reminiscent of mammary ducts and several mitotic figures (H&E, ×40 objective). **B:** Adenocarcinomas also developed from reconstituted glands consisting of *p53*-deficient epithelium in a wild-type fat pad. A poorly differentiated mammary carcinoma invading the adjacent skeletal muscle (H&E, ×20 objective). **C:** An adenocarcinoma arising from a $p53^{null/wt}$ transplant that has both acinar structures (**white arrow**) and a spindle cell component (×40 objective). **D:** Lung metastasis from a mammary carcinoma derived from a reconstituted gland consisting of $p53^{-/-}$ epithelium in a wild-type fat pad (H&E, ×10 objective).

mine whether loss of *p53* in the mammary epithelium was sufficient for the development of mammary carcinomas without the contribution of the *p53*-deficient stroma, reconstituted gland transplants were performed. Reconstituted mammary glands composed of either $p53^{-/-}$ epithelium and $p53^{+/+}$ stroma ($p53^{null/wt}$) or $p53^{+/+}$ epithelium and $p53^{+/+}$ stroma ($p53^{w/w}$) were transplanted into wild-type BALB/c hosts and monitored for tumor formation. Of the $p53^{null/wt}$-reconstituted glands that were accepted, 55% developed tumors (Table 1). Many of these tumors were histologically similar to the tumors derived from the BALB/c-$p53^{-/-}$ whole-gland transplants. Mammary tumors from $p53^{null/wt}$-reconstituted glands often exhibited sarcomatoid differentiation, invasive components, and distant metastases (Figure 5, A–C). The $p53^{wt/wt}$ transplants, which consisted of wild-type epithelium and stroma, did not develop tumors. Although the number of tumors that developed in the whole-gland transplants was greater than in $p53^{null/wt}$-reconstituted gland transplants, there was no statistical difference in latency or frequency between the transplant experiments ($P > 0.05$). Similar to the BALB/c-$p53^{-/-}$ whole gland transplants, 21% of the $p53^{null/wt}$-reconstituted gland transplants failed to engraft. This seemed to be dependent on the lack of *p53* in the epithelium because all of the $p53^{wt/wt}$ transplants were accepted and is consistent with recent experiments with transplants of *p53*-deficient mammary epithelium.[13]

Discussion

Given the large number of breast cancers with *p53* mutations and the prevalence of breast tumors in women with Li-Fraumeni syndrome,[15–17] it was surprising that the *p53*-deficient mice rarely developed mammary tumors.[18] Therefore, we sought to examine the effects of *p53* loss on the BALB/c strain that has been widely used for the study of the mammary gland and has been shown to be more susceptible to induction of mammary tumors.[7] BALB/c-$p53^{-/-}$ female mice did not develop mammary carcinomas, but stromal changes were frequently observed in the mammary gland. Early mortality because of lymphomas was likely to have precluded the development of mammary tumors. This is supported by the development of mammary carcinomas when *p53*-deficient mammary glands were transplanted into wild-type hosts (Table 1). Furthermore, transplantation of *p53*-deficient epithelium into wild-type fat pads also produced mammary carcinomas, suggesting that *p53* loss in the mammary epithelium is a critical step in tumorigenesis (Table 1).[13] The histology of mammary tumors observed in the BALB/c-*p53*-deficient mammary tissue is typical of spontaneous mammary tumors in mice[19] and does not exhibit unique histological features that have been observed in other genetically engineered mice.[20] Therefore, this knockout model of mammary tumorigenesis seems to reflect the acceleration of sporadic mammary tumors and their progression that is found in otherwise genetically normal mice.

In humans, Li-Fraumeni syndrome is an inherited predisposition to cancer development and more than half of affected families carry germline mutations in the *p53* tumor suppressor gene.[2] Tumors typically associated with this syndrome are early-onset breast carcinomas, osteosarcomas, soft-tissue sarcomas, brain tumors, and leukemias.[2,3,15–17] The BALB/c-$p53^{+/-}$ mice developed mammary carcinomas and other malignancies in a pattern and frequency similar to that reported for the Li-Fraumeni syndrome in humans (Figure 3A).[2–4,11,16] The breast cancers that arise in women from Li-Fraumeni families typically develop at mid-life, are highly aneuploid, and frequently lose the remaining wild-type *p53* allele.[9,17,18] Similarly, the mammary tumors in BALB/c-$p53^{+/-}$ mice developed near mid-life (latency of 8 to 14 months), were highly aneuploid, and frequently lost the wild-type *p53* allele (Figure 4). This frequent loss of the wild-type allele in mammary carcinomas from the BALB/c-$p53^{+/-}$ mice differs from the situation in lymphomas where more than half of lymphomas that developed in *p53*-heterozygous mice retained the wild-type allele.[21] Hence, loss of the wild-type *p53* allele may be required for tumor development in the mammary epithelium, but not in other tissues.

The loss of *BRCA1* has been linked to heightened risk of breast cancer, yet mutations in this tumor suppressor gene are infrequent in sporadic breast cancers. In *BRCA1* conditional knockout mice, where mammary tumors developed after 10 months, three out of four mammary tumors had also lost *p53*[22] suggesting that loss of both genes may contribute to tumorigenesis. However, none of the mammary carcinomas from BALB/c-$p53^{+/-}$ mice lost *BRCA1*, supporting the concept that loss of *p53* alone is a central and perhaps early event for initiation and progression of mammary tumors. Given that the *p53* and *BRCA1* genes lie 21 centimorgans apart on chromosome 11, it was surprising that loss of *BRCA1* was not seen in some of the tumors if genetic losses occurred randomly. Although the exact mechanism by which *p53* was deleted cannot be determined by this analysis, these data suggest that the tumor suppressive effects of p53 occur independent of *BRCA1*, and that loss of *BRCA1* was not required for the development of mammary tumors.

The high rate of mammary tumor development in the BALB/c *p53*-deficient mice compared to other *p53*-knockout strains is intriguing. Differences in tumor spectrum were reported between C57Bl/6x129/Sv, which primarily developed lymphomas, and pure 129/Sv, which readily developed testicular tumors.[18] It was suggested that the difference in tumor spectrums was related to the difference in strain-specific tumor susceptibilities. The 129/Sv mice have a relatively high incidence of teratocarcinomas[23] whereas the C57Bl/6 do not. Although the normal BALB/c inbred strain has a low incidence of spontaneous mammary tumors, it has been demonstrated that the BALB/c mammary epithelium is susceptible to genetic instability and radiation-induced mammary tumorigenesis.[7,8,24] A pivotal role of p53 in determining susceptibility of the mammary epithelium to tumor development is suggested by recent experiments demonstrating that p53 function is compromised in the normal BALB/c mammary

epithelium.[25] The heightened susceptibility of BALB/c mice to mammary tumor formation supports the existence of genetic modifiers that interact with *p53*-deficiency epistatically and predisposes to tissue-specific tumorigenesis. The BALB/c strain possesses a variant allele for *Cdkn2a* (p16/INK4a, p19/ARF)[26] that increases susceptibility of the BALB/c strain to plasmacytomas. P19/ARF-deficient mice are predisposed to tumor development, yet mammary carcinomas are rare.[27] This suggests that other unidentified modifier loci may be responsible for the mammary tumor phenotype in BALB/c-$p53^{+/-}$ mice. Identification of the genetic modifier gene(s) responsible for the heightened development of mammary carcinomas in BALB/c mice will be of particular importance because it may explain the variation in susceptibility to tumor development and tumor spectrum in different individuals with the same germline mutation in *p53*.

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